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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/527,844	03/17/2000	Timothy J. Barberich	4821-334-999	3697

20582 7590 06/30/2004

JONES DAY
51 Louisiana Aveue, N.W
WASHINGTON, DC 20001-2113

EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/30/2004

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/527,844
Filing Date: March 17, 2000
Appellant(s): BARBERICH ET AL.

Max Bachrach
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 30, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

The amendment after final rejection filed on December 30, 2003 with the Brief has been entered.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

4,831,031	Lowe	5-89
5,312,925	Allen et al	5-94

- Davis, Rick. CAPlus Abstract, copyrights 2002, American Chemical Society, "Ziprasidone" CNS Drugs (1997), 8(2), 152-159
- Parkash et al, "Metabloism and Excretion of a New Antipsychotic Drug, Ziprasidone, in Humans" Drug Metabolism and Disorders Vol 25(7), 863-869.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al.

Davis et al discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-HT2 and dopamine D2 receptors. Davis et al also discloses administration of this drug to patients. Davis further indicates that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia and in reducing anxiety in patients about to undergo dental surgery.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al in view of Lowe et al, Allen and Parkash et al.

Davis et al discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-HT2 and dopamine D2 receptors. Davis et al also discloses administration of this drug to patients. Davis further indicates that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia and in reducing anxiety in patients about to undergo dental surgery.

Davis does not specifically teach metabolites of ziprasidone, the amounts (i.e, dosage), or routes of administration as instantly claimed.

Lowe teaches that aryl piperazinyl (C2-C4) alkylene hetrocyclic compounds (including ziprasidone) and their pharmaceutically acceptable salts, known neuroleptic agents, can be administered orally, in form of tablets or capsules, or parenteraly, see col 3, line 54-col 4 line 33. Lowe also teaches that the daily dosage range of such agents are from 5 to 500 mg, see in particular col 4, lines 3-33, see also claim 1-9.

Allen specifically teaches the employment of ziprasidone hydrochloride as a neuroleptic agent.

Parkesh teaches the affinity of the sulfone and sulfoxide metabolites of ziprasidone for 5HT2 and D2 receptors.

It would have been obvious to one of ordinary skill in the art at the time of invention to employ ziprasidone or any of its known salts or metabolites, including the sulfone and sulfoxides, in a method for treating neuroleptic disorders.

One of ordinary skill in the art would have been motivated to employ ziprasidone or any of its known salts or metabolites in a method of treating neuroleptic disorders, because ziprasidone and ziprasidone hydrochloride are known in treating neuroleptic disorders and have been employed in treating anxiety, depression associated with schizophrenia and situational anxiety (i.e. anxiety prior to dental surgery). Further, employment of different salts and metabolites of a known active, as an alternative form of drug delivery, is within the skill of the artisan and therefore obvious.

(11) Response to Argument

Appellant's arguments filed on the Brief filed on December 30, 2003 (Brief) have been fully considered but they are not persuasive, because Appellant has not met their burden of proof required to overcome the rejections of record. Appellant's arguments lacks scientific and legal support to overcome the rejections of record. Accordingly, the rejections of record should be maintained.

Appellant's arguments are addressed below as they are directed to rejections of record.

A. Rejection of claims 1-4, 6-9 under 35 USC § 102 (b) over Davis should be maintained.

Appellant provides two sets of reasoning as to the incorrectness of this rejection, neither of which should be found persuasive.

a. Appellant first argues that Examiner's interpretation of the term "administration" is not correct because the step of administering of the instant compound requires existence of the compound outside of the patient (see *Brief* at page 10, 13).

Appellant offers that the methods of administering a metabolite of a compound are recognized by the Office and that such step amounts to a presumption that the metabolite exist outside of the patient. Appellant further relies on *Schering Corporation v. Geneva Pharmaceuticals*, Inc., 339 F.3d, 1373, 67 USPQ 2d 1664 (Fed. Cir. 2003) to support such conclusion. (see Brief at page 10-11).

Examiner has throughout the prosecution argued that Davis teaches administration of the drug to patients and that the administration of metabolites of ziprasidone, is inherent in to the administration of the parent drug ziprasidone (see Advisory Action filed on 9/12/2003; also see Final Rejection filed on 6/18/2003 at page 4). Appellant has not provided any evidence showing the contrary. Therefore, in view of all facts presented the claims should stand rejected.

Further, the fact that ziprasidone metabolite is synthesized *ex vivo*, is not viewed as the patentable subject matter. Rather, the patentability is assessed based on the entire claim which questions whether ziprasdione metablites can be used for treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin reuptake at 5-HT2 receptors. Davis teaches that ziprasdione itself has been used for this purpose. The ruling in *Zenith Laboratories Inc. v. Bristol-Myers Squibb Co.*, 30 USPQ2d 1285, 1289, provides that ziprasidone metabolites are necessarily and inevitably formed from the ziprasidone under normal condition.[1] Therefore, the method of administering ziprasdone metabolite for the claimed purpose is also disclosed. Appellant has not provided any

[1] In her Office Action issued 11/5/2002 at page 4, Examiner has relied on *Zenith Laboratories Inc. v. Bristol-Myers Squibb Co*, 30 USPQ2d 1285 (CAFC 1994) to argue that if ziprasidone itself is known to be useful in treating the instantly claimed diseases via the same mechanisms it would have been inherent and further obvious to employ the metabolites in lieu of ziprasidone in treating these same disorders.

evidence showing the contrary. Therefore, Appellant has not met his burden of proof and the claims should stand rejected.

In describing *Schering,*[2] Appellant acquiesce to the fact that a specific metabolite [DCL] [3] is "necessarily and inevitably formed from the parent [loratidine][4] under normal condition," and that a specific metabolite [such as DCL] is "a necessary consequence of administering the parent [such as loratadine] to patient." (see *Brief* at page 11).

In the instant case, the question before the Board is whether administering ziprasidone to a patient, such as those described in Davis, inherently anticipates the instant claims including the instant administering step of ziprasidone metabolite, because metabolites of ziprasidone are necessarily and inevitably formed under normal condition once ziprasidone is administered to a patient. In essence, does the teachings of Davis anticipate the instant claims when Davis provides that patients are administered ziprasidone for the same purpose as the instant claims.

Examiner believes that as set forth in *Zenith supra*, metabolites are found once the drug is in the body. Further, there are no evidence on the record that denies such outcome. Davis teaches that ziprasidone is administered for the same purpose as instantly claimed. Ziprasidone is necessarily metabolized in vivo to its metabolites. Therefore, Davis discloses administration of metabolites in vivo for the same purpose as those instantly claimed. Thus, the rejection should be maintained.

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[2] As described by Appellant, *Schering* concerned whether descarboethoxyloratadine (DCL), a metabolite of known drug loratadine, is patentable over its parent compound loratadine. The Court entertained the issue of whether a person would infringe a claim to a metabolite if that person ingests a compound that would metabolize to form the metabolite. See *Schering* at 1666 citing *Hochest-Roussel Pharms. Inc. v. Lehman*, 109 F3d 756, 759 (CAFC 1997), the court also relies on *Zenith Labs., Inc. v. Bristol Myers Squibb Co.*, 19 F3d 1418, 1421-22 (CAFC 1994) in addressing this issue. The Court then affirmed the conclusion of the lower court in that ingesting loratadine, the prior art, anticipates the metabolite of loratidine.

[3] DCL was the metabolite in question in *Schering*.

[4] Loratidine was the prior art of record used to inherently anticipate DCL in *Schering*.

Appellant has argued extensively that claims are not anticipated by Davis because as recited, they are directed to *ex vivo* synthesis and preparation of ziprasidone metabolites and that by itself provides a step of the existence of the metabolite outside of the patients body. (see *Brief* at page 11-12). In essence, Appellant appears to constructively present a product-by-process type argument, whereby, the product employed in the instant methodology, ziprasidone metabolites, are in fact prepared by a different *ex vivo* process.

In reply Examiner states that the fact that ziprasidone metabolite might have been prepared *ex vivo* is not determinative to the patentability of the methodology instantly claimed, because the product employed in a method claims may not be limited to the manipulations of the steps creating the product, only the structure implied by the steps, here, ziprasidone metabolites.

It has been a long standing policy that [the] patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe* , 227 USPQ 964, 966 (CAFC 1985). See MPEP 2113. Therefore, the method of administering ziprasdone metabolite, presumptively created by a different process, for the claimed purpose can not be patentable over the method of administering the parent drug for the same purpose. Appellant has not provided any evidence showing the contrary that even the ex vivo process would alter, in any way, the clinical outcome. Therefore, Appellant has not met his burden of proof and the claims should stand rejected.

b. With respect to rejection of claims 1-4, 6-9 under 35 USC § 102 (b) over Davis, Appellant's second argument is that claims directed to metabolites compound can be patentable over a prior art teaching of its parent compound when they are drafted in the form of a method of administering the metabolite (see *Brief* at page 11-12).

Appellant also argues that Court in *Schering* devoted an entire section of its opinion to a discussion of metabolite claims that are patentable. Appellant specifically cites the dicta, on page 7, of the Court's opinion that

> A skilled patent drafter...might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated forms... or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The [prior art] patent would not provide an enabling disclosure to anticipate such claims because, for instance, the [prior art] patent does not disclose isolation of DCL.

In response, Examiner does not dispute the truth of such statements in the dicta of *Schering*. Indeed a skilled patent drafter may fashion any claims over the prior art by incorporating a patentable subject matter into the claim, or otherwise provide such evidence on record to show unexpected results.

However, here, this is not the case. The statements relied on by the *Schering* Court is in reference as to such legal precedents wherein parties of interest met their burden of proof by a declaration of unexpected results or drafted such claims to clearly contain a subject matter patentable over the prior art.[5]

Here, Appellant has not met their burden of proof, because the scope of the rejected claims are directed to any metabolite of zisporidone and appellant has not

[5] See *In re Kratz*, 592, F.2d 1169, 1174 (CCPA 1979) wherein claims were directed to a specific isolated and purified form of natural constituent in strawberries and the prior art was a teaching for Fresh California Strawberries. Applicant submitted evidence in the form of Rule 132 Affidavit that established unexpected superiority of the claimed purified isolate. Also see *In re Seaborg*, 328 F2d, 996, 998-999 (CCPA 1964), wherein claims were directed to an isotope of americuium made by nuclear reaction. The prior art disclosed a similar nuclear reaction process. The court held that the prior art process would have at most one billionth of a gram of the isotope in the forty tons of radioactive material so that the isotope would have been undetectable.

provided any evidence showing such metabolites would not been created or provided the results described in Davis. Again, Davis teaches administering zisporidone to patients for the same intended use as instantly claimed. Formation of metabolites in vivo is implied in such teachings. Therefore, metabolites of zisporidone are inherently administered in vivo for the same purpose as claimed here. Appellant has provided no evidence showing the contrary. Accordingly, Examiner submits that the rejection of claims 1-4 and 6-9 under 35 USC § 102 (b) should be maintained.

B. **Rejection of claims 1-15, 50-53 under 35 USC § 103 (a) over Davis in view of Lowe and Allen should be maintained.**

Appellant's arguments with respect to this rejection have been fully considered but are not found persuasive. Appellant argues that none of the references teach ziprasidone metabolites. (see *Brief* at page 15).

Aside from the fact that Prakash clearly teaches ziprasidone metabolites (see entire article), Examiner states that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the rejection has been made over the combined teachings of the references, as they would have directed one of ordinary skill in the art. The combined teachings of the references meet all elements of the instant claims. Therefore, their individual shortcomings do not amount to a conclusion of nonobviousness.

In the instant case, one of ordinary skill in the art in possession of the cited references would have understood that (a) Davis teaches methodology of administering

ziprasidone for treating neuroleptic disorders, (b) Allen and Lowe teach methodologies of synthesizing effective salts of ziprasidone for therapeutic purposes, and (c) Parkish teaches that sulfone or sulfoxide metabolites are major metabolites of ziprasidone created by oxidation of sulfur atom and that they possess agonistic affinities towards 5HT2 and D2 receptors. Such agonistic properties would have motivated the skilled artisan to employ sulfone or sulfoxide metabolites in a therapeutic regimen absent information to the contrary. Accordingly, all elements of the instant claims are described in the art, because the intended use of the pending claims are described by Davis, the specific affinity of sulfone and sulfoxide for 5HT2 and D2 receptors are described by Parkish and the process of formulating pharmaceutical dosage forms, suitable dosing and therapeutic uses are described by Allen and Lowe.

Further, Examiner points out that obviousness does not require absolute predictability of success. For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). There is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co* ., 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co* ., 730 F.2d 1452, 1461, 221 USPQ 481, 488 (Fed.Cir. 1984). Here, Appellant simply has failed to meet the burden of proving nonobviousness.

Appellants' arguments that sulfone or sulfoxide metabolites have low affinities towards their receptors is not persuasive, because such statement is not an indication that they are void of any value for the same therapeutic purpose as ziprasidone. There is nothing on the record showing that the instantly claimed metabolites would have provided unexpected therapeutic results. Nor is there any evidence on record that ziprasidone's metabolites cannot be used for their antipsychotic effects.

Again, Examiner reiterates that all that is required for an obviousness rejection is a reasonable expectation of success. Examiner has taken the position that the fact that sulfone or sulfoxide metabolites of ziprasidone have affinity towards 5HT2 and D2 receptors provide a reasonable expectation of success for one of ordinary skill in the art to employ them for the same therapeutic purposes as their parent drug ziprasidone. Therefore, such use would have been well within the level of an ordinary skill in the art at the time of invention.

Appellant goes on to assert, relying on Hawley's Condensed Chemical Dictionary, that the teachings of Lowe and Allen are not relevant because they teach ziprasidone's salts and a salt form of a compound is completely different from a metabolite of the compound. (see *Brief* at page 15).

In reply Examiner states that such line of arguments are not persuasive, because the instant pending claims do not exclude the salts or metabolites described in the cited reference. First, Prakash explicitly teaches ziprasidone metabolites to include oxindindole-acetic acids, oxidates, sulfones and sulfoxides. Second, Allen and Lowe provide for methods of preparing ziprasidone salts *ex vivo* to formulate pharmaceutical

dosage forms. Metabolites of Prakash are indeed a salt form of ziprasidone. Therefore, the combined teachings of the reference would have also provided for methods of using various forms of metabolites including sulfone or sulfoxides of ziprasidone.

Appellant has also presented arguments that in order for zipradidone metabolites to have *in vivo* activity, ziprasidone itself should have been inactive. (see *Brief* at page 18). Accordingly, appellant draws the conclusion that ziprasidone cannot result in the same activity as the administration of a ziprasidione metabolites. *Id.*

Again these lines of arguments are neither supported by any evidence, nor are they commensurate with the scope of the claims. As the initial matter, the pending claims are not directed to enhanced clinical effects of ziprasidone with regards to ziprasidones' metabolites. Providing any clinical effect would have been within the scope of the instant claims. Since Prakash provides for affinity of metabolites towards 5HT2 and D2 receptors, there would have been adequate reasonable expectation of success for the use of sulfone or sulfoxide metabolites for the same reasons as ziprasidone.

Second, appellant's assertion that ziprasidone should have been inactive *in vivo* for its metabolites to provide therapeutic effects is simply incorrect. Appellant appears to be referring to the concept of prodrugs and their use in the art. The instant claims are not limited to such features. Therefore, appellant's arguments are not applicable.

Additionally, aside from the fact that Appellant's has not provided a scintilla of evidence supporting an inactivity assertion as it pertains to the instant claims, Examiner states that there are many drugs currently in market that not only exist in an active form,

but also are metabolized into additional active metabolites when *in vivo*. Besides from DSL, the active metabolite in *Schering*, active drugs creating active metabolites *in vivo* include such commonly known drugs as: procainamide and its active metabolite, N-acetyl procainamide; allopurinol and its active metabolite oxipurinol; morphine, and its active metabolite, morphine-6-glucuronide. Thus, Appellant's assertion, and conclusion, that for ziprasidone metabolites to have *in vivo* activity, ziprasidone itself should have been inactive, appears to lack scientific foundation. For the reasons set forth above, the rejection of claims 1-15, 50-53 should be maintained.

C. Appellant's assertion about Examiner's reliance on Zenith[6] (see *Brief* at page 19).

Appellant's assertion about Examiners' reliance on *Zenith* is noted. Appellant has argued throughout the prosecution that *Zenith* is not applicable in this case because it neither discloses any biological activity of ziprasidone or its metabolites, nor is it concerned whether the claims of a patent were anticipated or obvious. Appellant adds that *Zenith* was a ruling only in the context of a patent infringement analysis, not patentability determination. *Id.*

In response, Examiner reiterates that *Zenith* was used as the controlling case on point. The fact that it does not provide any specific teaching about ziprasidone is not relevant because the Court in *Zenith* faced a similar issue as the instant case.

Further, in response to Appellant's assertion that *Zenith* was a ruling in the context of a patent infringement analysis, not patentability determination, Examiner states that it has been well recognized in the patent law "that which would literally infringe if later in

time anticipates if earlier," *Bristol-Myers Squibb Co v. Ben Venue Lab, Inc.*, 246 F3d 1368, 1378 (Fed. Cir. 2001). Thus, Examiner sees no reason to neglect the general rule of patent law established *in Zenith* as it pertains to an anticipation argument based on inherency. Thus, the rule should be applicable to the instant case because the inherency rejection of record is the essential issue in controversy.

For the above reasons, it is believed that the rejections should be sustained.

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[6] *See supra* No. 4.

Respectfully submitted,

Shahnam Sharareh, JD, PharmD

ss
June 28, 2004

Conferees

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

JONES DAY
51 Louisiana Aveue, N.W
WASHINGTON, DC 20001-2113